Editor-in-Chief : Atul Goel (INDIA)
Open Access HTML Format
For entire Editorial Board visit : http://www.jcvjs.com/editorialboard.asp
Journal of Craniovertebral Junction and Spine

Original Article

The impact of steroids, methotrexate, and biologics on clinical and radiographic outcomes in patients with rheumatoid arthritis undergoing fusions at the craniovertebral junction

Ryan Khanna, Brian J. Dlouhy[1], Zachary A. Smith, Sandi K. Lam[2], Tyler R. Koski, Nader S. Dahdaleh

Departments of Neurological Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois, [1]Neurological Surgery, University of Iowa, Carver School of Medicine, Iowa City, Iowa, [2]Division of Pediatric Neurosurgery, Texas Children's Hospital, Houston, Texas, United States

Corresponding author: Dr. Nader S. Dahdaleh, Department of Neurologic Surgery, Northwestern University, 676 N. St. Clair, Suite 2210, Chicago, Illinois-60611, United States. E-mail: nader.dahdaleh@northwestern.edu

Journal of Craniovertebral Junction and Spine 2015, 6:16

Abstract

Objective: Rheumatoid arthritis (RA) is an inflammatory disease that affects the craniovertebral junction (CVJ). Patients may suffer from atlantoaxial instability (AAI) and basilar invagination (BI) with variable presentations ranging from pain to quadriparesis. Managing these patients is often challenging due to their chronic use of steroids, methotrexate, and biologics; which impedes bone and wound healing. We report our experience with the surgical management of these patients undergoing fusions at the CVJ. **Materials and Methods:** We conducted a retrospective study identifying all patients with the diagnosis of RA who underwent spinal fusions at our institution over the past 11 years. A total of 205 patients were identified amongst which 18 patients (8.8%) who underwent 20 fusions involving the CVJ. Demographic, clinical, and radiographic data were analyzed. **Results:** Five patients had AAI and 13 patients had BI. Two patients with C1-2 fusions underwent reoperation: One for pseudoarthrosis and one for BI. The average preoperative Nurick was 1.4 and improved to 0.5 postoperatively ($P < 0.001$). After conducting analyses stratified by dichotomous preoperative variables, the presence of steroids, methotrexate, biologics, and prednisone dosage less than 7.5 mg did not affect outcomes. Prednisone dosages ≥7.5 mg had significantly smaller improvements in Nurick score compared to patients not on steroids or on prednisone dosages <7.5 mg (0.40 vs 1.36, $P = 0.042$). Similarly, patients on biologics had significantly smaller improvements in Nurick score compared to patients not on biologics (0.27 vs 1.16, $P = 0.038$). **Conclusion:** Fusions at the CVJ in patients with RA on daily prednisone dosages of less than 7.5 mg and/or methotrexate can be performed safely with good outcomes, fusion rates, and acceptable complication profiles. Daily prednisone dosages of more than 7.5 mg or biologics may impact clinical outcomes.

Key words: Biologics, craniovertebral junction, methotrexate, rheumatoid arthritis, steroids

Access this article online	
Quick Response Code:	Website: www.jcvjs.com
	DOI: 10.4103/0974-8237.156044

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, relapsing inflammatory disease that primarily affects diarthrodial joints and periarticular bone, and results in substantial deformity and functional impairment.[1] It affects 1.3 million adults in the United States[2] and has a worldwide prevalence of approximately 1-2%.[3,4] Knowledge of this disease's propensity in involving the cervical

spine and in particular the craniovertebral junction (CVJ) has been known since the 18th and 19th century,[5] and involvement of the cervical spine is common with a prevalence ranging from 17 to 80%.[3,4]

Classically, RA primarily affects the upper cervical spine or CVJ resulting in atlantoaxial subluxation, basilar invagination (BI; or cranial settling). To a lesser extent, it also affects the subaxial cervical spine resulting in subaxial subluxation. A combination of these pathologies can also be encountered in RA patients.[6] Symptoms can include pain, myelopathy, cranial nerve palsies, and/or signs of vascular insufficiency.[7] In recent years, early referral and the introduction of disease-modifying antirheumatic medications (DMARDs) such as methotrexate have led to substantial long-term improvements in patients with RA.[8,9]

Even with changes in treatment, a large number of patients with rheumatoid spine still require surgical intervention.[3] Since most symptoms are caused by instability, fusion at the CVJ is often the treatment of choice for patients with rheumatoid cervical spine presenting with atlantoaxial instability (AAI), cranial setting, and/or progressive neurological decline.[10] However, the decision to undergo surgery should be weighed heavily as these surgical procedures can result in complications such as pseudoarthrosis and adjacent segment instability,[11] often times related to baseline osteopenia or osteoporosis. The prevailing hypothesis for these complications is that RA results from a humoral autoimmune response arising from exposure to an environmental agent in a genetically predisposed individual. Subsequently, autoantibodies such as rheumatoid factor form, which lead to further activation of the complement system and neutrophils. Ultimately, cytokines and digestive enzymes are secreted that result in osteoclast activation and ultimately destruction of adjacent cartilage, tendons, and bone; also resulting in ligamentous laxity, and hence instability.[6]

Additionally, these patients are often on various rheumatoid medications including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, methotrexate, and biological agents (tumor necrosis factor-α and interleukin-1 antagonists), which reduces success of fusion. It is often times impractical to stop these agents due to flare-up, but corticosteroids have been shown to impair bone and wound healing,[12] methotrexate may affect bone healing,[13] and biologics increase the risk of opportunistic infections.[14]

Past studies have shown that surgical outcomes are better in patients with less preoperative impairment and that outcomes of surgery for rheumatoid cervical spine differ based on different diagnoses.[6,10] Surgical reconstruction has been demonstrated to improve patients' health-related quality of life, but how these medications may affect outcomes has not been investigated.[15] Our study aims to be the first to investigate how RA medications including corticosteroids, methotrexate, and biologics may affect clinical and radiological outcomes following fusions at the CVJ in the rheumatoid spine.

MATERIALS AND METHODS

All data for this study was obtained using an institutional electronic data warehouse (EDW) after obtaining approval from the investigational review board of our hospital. Current Procedural Terminology (CPT) codes were used to identify all spinal fusions at our institution from May 2003 to January 2013. The International Classification of Diseases (ICD) codes of 714.0 and 714.2 were used to identify patients with the diagnosis of RA. A total of 205 patients with RA who underwent spinal surgeries were identified. Amongst that cohort, 18 patients (three men and 15 women) who underwent 20 fusions at the CVJ were included in the study.

Demographics were collected using electronic chart review. The use of corticosteroids, methotrexate, and biologics was noted. Allograft was used in all surgeries, and the use of autograft and bone morphogenic protein (BMP) was collected. The primary outcome in this study was clinical using Nurick scores,[16] Ranawat scores,[17] and Odom's criteria[18] that were collected retrospectively by a blinded unbiased observer. O-C2 angle [Figure 1] was measured from X-rays preoperatively, within 1week postoperatively, and at the final follow-up visit. Best efforts by the surgeon were undertaken to maintain the O-C2 angle because changes are associated with dysphagia and dyspnea.[19] Fusions were assessed using computed tomography (CT) obtained during the last follow-up visit.

The data were analyzed using *t*-test, analysis of variance (ANOVA), and logistic univariable regression. All analyses were done using Statistical Package for Social Sciences (SPSS), version 22.0 (IBM, Armonk, NY). The level of significance was set at $P < 0.05$.

RESULTS

The mean age was 61.7 years. Fifteen out of 18 patients were females. Five patients had AAI [Figure 2] and 13 patients had BI [Figure 3]. Patients with BI underwent occipitocervical fusions,

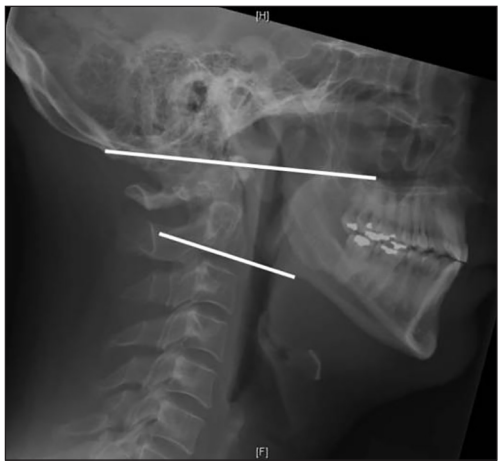

Figure 1: Lateral X-ray of the cervical spine demonstrating the O-C2 angle. It is the angle formed by McGregor's line and the inferior endplate of C2

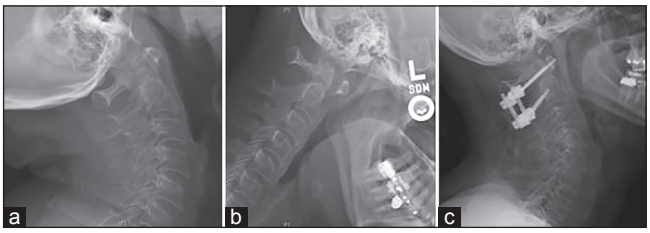

Figure 2: A 60-year-old woman with rheumatoid arthritis on prednisone and methotrexate presented with 6 months' history of progressively severe neck pain and numbness in the lower extremities. Dynamic lateral X-rays of the cervical spine showed atlantoaxial instability (a and b). The patient was braced with a Miami J collar with no improvement of her symptoms. She underwent posterior atlantoaxial fusion (c) with resolution of her symptoms

while patients with AAI underwent C1/C2 fusions. The average levels fused were 6.1 ± 4.5 levels (mean ± standard deviation).

The patients' average follow-up period was 35.5 ± 30.1 months (mean ± standard deviation). None of the 18 patients died during follow-up. Average length of stay was 6.1 ± 4.5 days. BMP was used in 10 out of 18 surgeries (55.6%) and autograft was used in seven out of 18 surgeries (38.9%). Twelve of 18 (66.7%) patients were on chronic prednisone with an average daily dose of 9 mg at the time of surgery. Five out of 18 patients (27.8%) were on methotrexate and six out of 18 patients (33%) were on biologics at the time of surgery.

The mean preoperative O-C2 angles were 13.9° ± 10.5, postoperative O-C2 angles were 13.7° ± 10.3, and angles recorded during final clinical visit had a mean of 13.4° ± 11.2. These differences were not significant ($P = 0.636$). The average preoperative Nurick was 1.4 and improved to 0.5 postoperatively ($P < 0.001$). According to the Odom scale, five patients had an excellent outcome, six good, six fair, and one had a poor outcome. There was also improvement in the Ranawat scale [Table 1].

After conducting analyses stratified by dichotomous preoperative variables, the presence of steroids, methotrexate, biologics, and prednisone dosage less than 7.5 mg did not affect outcomes. Prednisone dosages ≥7.5 mg had significantly smaller improvements in Nurick score compared to patients not on steroids or on prednisone dosages <7.5 mg (0.40 vs 1.36, $P = 0.042$). Similarly, patients on biologics had significantly smaller improvements in Nurick score compared to patients not on biologics (0.27 vs 1.16, $P = 0.038$). Preoperative and postoperative Nurick scores for these patients can be seen in Tables 2 and 3. Importantly, stratification revealed no significant differences in length of stay changes in O-C2 angles, Ranawat, or Odom when stratified by dichotomous preoperative variables. The use of BMP or autograft had no impact on any of the clinical outcomes studied including Nurick, Odom, or Ranawat scores or on fusion rates ($P > 0.05$).

Complications and reoperations

Two patients with C1-C2 fusions underwent reoperation: One for pseudoarthrosis and one for BI. The first patient was on

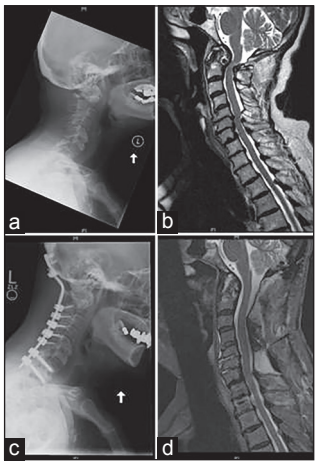

Figure 3: A 72-year-old patient with rheumatoid arthritis on prednisone presented with a 1-year history of progressively severe neck pain and progressive quadriparesis. Lateral X-ray (a) and lateral sagittal T2-weighted imaging (b) showed cranial settling with BI and cervicomedullary compression as well as subaxial cervical stenosis. She was placed in crown halo traction and underwent C0 to T2 fusion and decompression (c) with restoration of appropriate alignment and resolution of the compression at the CVJ and subaxially (d)

Table 1: Ranawat scores: Preoperative versus postoperative

Ranawat	Description	Preoperative (%)	Postoperative (%)
1	No neural deficit	17	55
2	Subjective weakness, dysesthesia, and hyperreflexia	22	6
3a	Objective weakness and long tract signs; patient ambulatory	39	39
3b	Objective weakness and long tract signs; patient no longer ambulatory	22	0

Table 2: Nurick scores: Preoperative versus postoperative while on prednisone

Prednisone	Preoperative	Postoperative	Change
<7.5 g/day (*n*=13)	1.38	0.27	1.36
>7.5 g/day (*n*=5)	1.60	1.20	0.40

Table 3: Nurick scores: Preoperative versus postoperative while on biologics

Biologics	Preoperative	Postoperative	Change
No Biologics (*n*=12)	1.83	0.67	1.16
Biologics (*n*=6)	0.67	0.40	0.27

10 mg of prednisone daily, but no methotrexate or biologics at the time of surgery. Postoperatively, she had persistent

dysphagia and posterior cervical pain and after diagnosis of pseudoarthrosis 7 years after original surgery, required a revision of the original fusion with extension from C2-T2. On second operation, the patient improved Nurick score from 2 to 1 and had a "good" Odom score at final follow-up.

The second patient required reoperation due to BI. At the time of the original surgery, the patient was on 15 mg of prednisone daily and biologics, but no methotrexate. Three years after original surgery, the patient had an extension of occiput-C4, and improved Nurick from 2 to 1 and had a "good" Odom score at final follow-up. Finally, one patient required a wound revision.

DISCUSSION

The synovial joints between the transverse atlantal ligament and the odontoid process, alar ligament, as well as the joints between the anterior arch of the atlas and the odontoid are frequently affected in RA patients. With chronic inflammation, the transverse ligament weakens and eventually ruptures resulting in atlantoaxial subluxation. Destruction and collapse of the atlanto-occipital, atlantoaxial joints, and lateral atlantal masses; results in the odontoid process telescoping rostrally resulting in occipitoatlantoaxial impaction or BI (or cranial settling).[20,21] Less frequently, subaxial subluxation or a combination of these deformities can also take place.[6] Nonoperative management of these conditions is usually ineffective.[22-25] The progressive nature of RA leads to myelopathy and severe occipital/neck pain,[17,26] and occasionally can lead to quadriplegia, respiratory muscle paralysis, and death. Due to the resultant instability at the CVJ, upper cervical spine fusion (occipitocervical fusion or atlantoaxial fusion) is oftentimes pursued. These procedures are complicated, difficult, and risky in the rheumatoid spine. Pseudoarthrosis and mortality rates are oftentimes not insignificant.[10]

Previous studies have investigated outcomes of performing cervical spine fusions on the upper cervical spine on patients with RA. These have demonstrated that there are clear quality of life improvements seen with these procedures,[15] and outcomes depend on severity of condition at initial presentation.[10] Patients with less preoperative impairment generally have better surgical outcomes,[27] thus intervening early and before BI occurs has been shown to reduce the risk of complications and increase long-term outcomes.

Perioperative management of these patients can be challenging.[28] These patients are often on many medications including NSAIDs, steroids, DMARDs, and biologics that reduce bone healing and increase other complication rates.[12-14] However, due to the high morbidity of RA flare-ups, it can be very difficult to wean or stop these medications. In this study, we examine the outcomes of fusions at the upper cervical spine or CVJ in patients with RA, shedding light on how steroids, methotrexate, and biologics may affect outcomes. To our knowledge, this is the first study to examine this association.

Our study demonstrates that fusions at the CVJ can be performed safely with acceptable outcomes and complication profiles in patients with RA on chronic steroids, methotrexate, and biologics. Nurick, Ranawat, and Odom scores all improved postoperatively. Additionally, O-C2 angles did not change throughout follow-up indicating no settling and the maintenance of alignment. All patients, except for one, achieved fusions. When stratified by medications, the only significant differences were the decrease in improvement of Nurick scores for patients on a greater than 7.5 mg of daily prednisone and patients on biologics. We hypothesize this difference occurs due to a combination of severe RA and effects of medication. Patients are often placed on higher doses of steroids and biologics after they have failed initial therapy including DMARDs.[29-31] However, even though these patients were associated with less improvement than patients on smaller doses of steroids or not on biologics, they still improved. Another possible contributor to a smaller improvement for patients on biologicsis that these patients had lower Nurick scores at baseline, which limited the improvement of that cohort. These lower scores correlate to less impairment, which may reflect the effects of the biologics. However, further investigation is required.

Limitations to this study include lack of a control group, retrospective design, and a small sample size.

CONCLUSION

Fusions at the CVJ in patients with RA on daily prednisone dosages of less than 7.5 mg and/or methotrexate can be performed safely with good outcomes, fusion rates, and acceptable complication profiles. Daily prednisone dosages of more than 7.5 mg or biologics may impact clinical outcomes.

REFERENCES

1. Koopman WJ. Prospects for autoimmune disease: Research advances in rheumatoid arthritis. JAMA 2001;285:648-50.
2. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, *et al.* National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58:15-25.
3. Stein BE, Hassanzadeh H, Jain A, Lemma MA, Cohen DB, Kebaish KM. Changing trends in cervical spine fusions in patients with rheumatoid arthritis. Spine (Phila Pa 1976) 2014;39:1178-82.
4. Nguyen HV, Ludwig SC, Silber J, Gelb DE, Anderson PA, Frank L, *et al.* Rheumatoid arthritis of the cervical spine. Spine J 2004;4:329-34.
5. Hansen SE. The recognition of rheumatoid arthritis in the eighteenth century. The contribution of Linne and Boissier de la Croix de Sauvages. Scand J Rheumatol 1993;22:178-82.
6. Mallory GW, Halasz SR, Clarke MJ. Advances in the treatment of cervical rheumatoid: Less surgery and less morbidity. World J Orthop 2014;5:292-303.
7. Gurley JP, Bell GR. The surgical management of patients with rheumatoid cervical spine disease. Rheum Dis Clin North Am 1997;23:317-32.
8. Ward MM. Decreases in rates of hospitalizations for manifestations of severe rheumatoid arthritis, 1983-2001. Arthritis Rheum 2004;50:1122-31.
9. Finckh A, Choi HK, Wolfe F. Progression of radiographic joint damage in different eras: Trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. Ann Rheum Dis 2006;65:1192-7.
10. Miyamoto H, Sumi M, Uno K. Outcome of surgery for rheumatoid cervical spine at one institute over three decades. Spine J 2013;13:1477-84.

11. Crawford CH 3rd, Carreon LY, Djurasovic M, Glassman SD. Lumbar fusion outcomes in patients with rheumatoid arthritis. Eur Spine J 2008;17:822-5.
12. Howe CR, Gardner GC, Kadel NJ. Perioperative medication management for the patient with rheumatoid arthritis. J Am Acad Orthop Surg 2006;14:544-51.
13. Gerster JC, Bossy R, Dudler J. Bone non-union after osteotomy in patients treated with methotrexate. J Rheumatol 1999;26:2695-7.
14. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, *et al.* Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Rheum 2006;55:333-7.
15. Uehara M, Takahashi J, Hirabayashi H, Ogihara N, Mukaiyama K, Kuraishi S, *et al.* Evaluation of clinical results and quality of life after surgical reconstruction for rheumatoid cervical spine. Spine J 2013;13:391-6.
16. Nurick S. The pathogenesis of the spinal cord disorder associated with cervical spondylosis. Brain 1972;95:87-100.
17. Ranawat CS, O'Leary P, Pellicci P, Tsairis P, Marchisello P, Dorr L. Cervical spine fusion in rheumatoid arthritis. J Bone Joint Surg Am 1979;61:1003-10.
18. Odom GL, Finney W, Woodhall B. Cervical disk lesions. J Am Med Assoc 1958;166:23-8.
19. Miyata M, Neo M, Fujibayashi S, Ito H, Takemoto M, Nakamura T. O-C2 angle as a predictor of dyspnea and/or dysphagia after occipitocervical fusion. Spine (Phila Pa 1976) 2009;34:184-8.
20. Kim DH, Hilibrand AS. Rheumatoid arthritis in the cervical spine. J Am Acad Orthop Surg 2005;13:463-74.
21. Rawlins BA, Girardi FP, Boachie-Adjei O. Rheumatoid arthritis of the cervical spine. Rheum Dis Clin North Am 1998;24:55-65.
22. Casey AT, Crockard HA, Bland JM, Stevens J, Moskovich R, Ransford A. Predictors of outcome in the quadriparetic nonambulatory myelopathic patient with rheumatoid arthritis: A prospective study of 55 surgically treated Ranawat class IIIb patients. J Neurosurg 1996;85:574-81.
23. Fujiwara K, Owaki H, Fujimoto M, Yonenobu K, Ochi T. A long-term follow-up study of cervical lesions in rheumatoid arthritis. J Spinal Disord 2000;13:519-26.
24. Boden SD. Rheumatoid arthritis of the cervical spine. Surgical decision making based on predictors of paralysis and recovery. Spine (Phila Pa 1976) 1994;19:2275-80.
25. Sunahara N, Matsunaga S, Mori T, Ijiri K, Sakou T. Clinical course of conservatively managed rheumatoid arthritis patients with myelopathy. Spine (Phila Pa 1976) 1997;22:2603-7.
26. Clark CR. Rheumatoid involvement of the cervical spine. An overview. Spine (Phila Pa 1976) 1994;19:2257-8.
27. Schmitt-Sody M, Kirchhoff C, Buhmann S, Metz P, Birkenmaier C, Troullier H, *et al.* Timing of cervical spine stabilisation and outcome in patients with rheumatoid arthritis. Int Orthop 2008;32:511-6.
28. Krause ML, Matteson EL. Perioperative management of the patient with rheumatoid arthritis. World J Orthop 2014;5:283-91.
29. Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, *et al.* Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: A systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976-86.
30. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, *et al.* A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: A Cochrane overview. Can Med Assoc J 2009;181:787-96.
31. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafstrom I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: A two-year randomized trial. Arthritis Rheum 2005;52:3360-70.

How to cite this article: Khanna R, Dlouhy BJ, Smith ZA, Lam SK, Koski TR, Dahdaleh NS. The impact of steroids, methotrexate, and biologics on clinical and radiographic outcomes in patients with rheumatoid arthritis undergoing fusions at the craniovertebral junction. J Craniovert Jun Spine 2015;6:60-4.

Source of Support: Nil, **Conflict of Interest:** None declared.